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CLARK & ELBING LLP 101 FEDERAL STREET BOSTON, MA 02110			EXAMINER KINGAN, TIMOTHY G	
			ART UNIT	PAPER NUMBER
			1797	
			NOTIFICATION DATE	DELIVERY MODE
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentadministrator@clarkelbing.com

### Office Action Summary

**Application No.**

10/519,014

**Applicant(s)**

FLANDRE ET AL.

**Examiner**

TIMOTHY G. KINGAN

**Art Unit**

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --  
**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 21 December 2004.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-27 is/are pending in the application.
- 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 1-27 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some \* c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO/SE-08)  
Paper No(s)/Mail Date 12/21/2004 and 09/09/2005
- 4) ☐ Interview Summary (PTO-413)  
Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

#### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claim 12 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In the instant claim it is not clear if "individually addressed" refers to the arrays of an individual electrode or the individual fingers of each interdigitated array.

#### ***Claim Rejections - 35 USC § 102***

3. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless –

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

4. Claims 10-13, 17, 21-25 and 27 are rejected under 35 U.S.C. 102(b) as being anticipated by T.G. Ewart and T. Bogle, U.S. Patent 5,922,537 (herein after Ewart). For Claim 10, Ewart teaches capacitive biosensors (col 14, lines 10-11) for detecting proteins and DNA (Table 1) (target sample), in which reporters of magnetic particles function as the labeling entities (col 3, line 66 to col 4, line 9) (conductive labels being couplable to target sample), biosensors comprising electrodes (col 16, lines 23-25) the surfaces of which are passivated (insulated/made non-conductive) with silicon nitride

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(col 14, lines 54-56; col 16, lines 28-30) or parylene polymer (col 14, lines 2-4) and coated with silica to facilitate covalent linking of molecules (able to selectively bind a capacitive sensor element). Further, a sensor may comprise an interdigitated electrode (Fig. 14; col 15, lines 31-33) (at least two electrodes) in which capacitances are measured with a sensing circuit comprising a Wheatstone Bridge (application of electrical signal to sensor) (col 18, lines 44-54; Fig. 10).

For Claim 11, Ewart teaches measuring differential capacitance related to addition or removal of particles that alter the conductive properties of the test surface (col 9, lines 13-21 and col 5, lines 18-21) (conductive labels coupled to target sample).

For Claim 12, Ewart teaches an electrode comprising an array of interdigitated electrodes (parallel fingers), each pair of arrays (anodes and cathodes) being individually addressed (Fig. 1).

For Claim 13, Ewart teaches a thin film device for capacitance measurements comprising coplanar interdigitated capacitor plates (col 15, lines 31-33; data: Fig. 14) (all fingers of an anode or cathode being short-circuited).

For Claim 17, Ewart teaches a capacitive sensor comprising semiconductor substrate functionalized to react with amino silanes (col 6, lines 59-62).

For Claim 21, Ewart teaches a Wheatstone Bridge circuit for measuring differential changes in sensor capacitance (a comparator unit) (col 18, lines 40-47; Fig. 10).

For Claim 22, Ewart teaches a capacitive sensor with a phosphorescence sensor (optical detector) comprising an optical waveguide for focusing light on the phosphorescence detector (col 17, lines 47-50).

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For Claim 23, Ewart teaches a capacitive biosensor with the use of magnetic particles as labels for targets, the presence of such particles being measured as a change in inductance (col 2, lines 16-19) (a magnetic sensor).

For Claims 24 and 27, Ewart teaches a capacitive sensor with electrodes made of titanium (a non-noble metal) with or without a gold metallization layer (col 14, lines 50-52).

For Claim 25, Ewart teaches a capacitive sensor, the mini-wells between electrodes being coated with a dielectric layer (non-conducting surface) of silicon nitride (col 16, lines 26-30).

### ***Claim Rejections - 35 USC § 103***

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

6. The factual inquiries set forth in *Graham v. John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

7. Claims 1-5 are rejected under 35 U.S.C. 103(a) as being unpatentable over S-J. Park et al., Science, 295: 1503-1506, 2002.

For Claim 1, Park teaches a method of electrically detecting gold nanoparticle-labeled (conductive labels) (abstract) nucleic acid hybrids comprising immobilizing capture oligonucleotides on an activated surface of a substrate (p. 1504, ¶ 2) and then exposing to nanoparticle-labeled probe oligonucleotides (p. 1504, ¶ 3) (binding target sample target sample to selective sites, labeled with conductive labels, to determine presence of target). The method of Park does not teach non-ohmic sensing (rather, changes in resistance are measured), but Park teaches that, in principle, capacitance measurements can be made (p. 1503, ¶ 2). One of ordinary skill in the art at the time of invention would have found obvious to use such capacitive detection as suggested by Park in order to provide flexibility in sample preparation, since nanoparticles of different sizes may be used to achieve a change in the dielectric without requirement for closing contact of the electrodes.

For Claims 2-3, Park does not teach a preliminary capacitance measurement. It would have been obvious to one of ordinary skill in the art to use such preliminary measurement in order to test for any change in capacitance associated with immobilization of probe, and, in so doing, better isolate the signal associated hybridization of labeled target. Such separate measurements immediately suggest comparison.

For Claims 4-5, Park teaches a method of detection comprising treatment of bound label with silver enhancer solution (p. 1504, ¶ 3) during which metallic silver is deposited

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at nucleating nanoparticle sites (labels enlarged by silver precipitation prior to the sensing step) (Fig. 3).

8. Claims 6 and 7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Park as applied to claim 1 above, and further in view of C. Berggren et al., *Electroanalysis* 13(3): 173-180, 2001.

For Claim 6, Park is silent on measurement of capacitance as a function of frequency. Berggren teaches capacitive biosensors in which impedance spectra are obtained by measurements at different AC frequencies (p. 179, ¶ 1). It would have been obvious to one of ordinary skill in the art to use measurements at different frequencies in order to characterize an unknown system within the method of Park to optimize the capacitive contribution to impedance, and, in so doing optimize parameters of the measurement for detecting changes in the dielectric.

For Claim 7, Park does not teach measurement of global impedance. Berggren teaches measurement of both in-phase (real part) and out-of-phase impedance (p. 176, ¶ 1) (together, global impedance) and the affects of non-specific binding on in-phase impedance (using the real part of global impedance) (p. 176, ¶ 1). It would have been obvious to one of ordinary skill in the art to separately consider the two components of impedance within the teaching of Berggren in order to distinguish between capacitive changes associated with non-specific binding and binding or hybridization of labeled target and to use such information in optimizing the experimental conditions of binding steps in the method of Park.

9. Claim 8 is rejected under 35 U.S.C. 103(a) as being unpatentable over Park as applied to claim 1 above, and further in view of T.A. Taton et al., Science 289: 1757-1760, 2000. The method of Park is silent on use of optical detection. Taton teaches a method of detection of gold nanoparticle-labeled targets (conductive labels) hybridized to probe immobilized on a biosensor comprising the use of a flatbed scanner (optical detection) (Fig. 1 and caption). It would have been obvious to one of ordinary skill in the art to use optical detection according to the teaching of Taton within the method of Park in order to provide for detection with simple and inexpensive equipment that is capable of high spatial and gray-scale resolution and is commonly available in laboratories.

10. Claim 9 is rejected under 35 U.S.C. 103(a) as being unpatentable over Park as applied to claim 1 above, and further in view of Ewart. Park is silent on detection of magnetic or radioactive emissions associated with label. Ewart teaches use of detection based on magnetic separation (col 1, lines 55-57 and col 2, lines 13-19). It would have been obvious to one of ordinary skill in the art to use detection of magnetic properties (change in inductance) of particles according to Ewart in the method of Park in order to provide the flexibility of an additional modality in detection that expands or has a different range of sensitivity with respect to bound nanoparticles or to provide for use of standard detection methods such as magnetic tape read head or Hall effect detector.



11. Claim 14 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart in further view of M. Taguchi et al., U.S. Patent Application Publication 20020050173 (herein after Taguchi).

For Claim 14, Ewart is silent on electrodes as an array of crossed fingers. Such arrays are well known, for instance in pressure-sensitive transducers. Taguchi teaches electrodes comprising electrodes in which at least one electrode portion crosses a plurality of electrode portions of opposite polarity [0006]. One of ordinary skill in the art would find obvious to use such arrays according to the teaching of Taguchi in the device of Ewart for increasing the spatial resolution in transducing signal associated with changing resistance or capacitive component of impedance. One of ordinary skill in the art would find desirable such increase in resolution in order to separately address multiple reactive sites with a single array of crossed fingers.

12. Claim 15 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart as applied to claim 10 above, and further in view of M. DeSilva et al., Biosensors and Bioelectronics 10: 675-682, 1995 (herein after DeSilva).

For Claim 15, Ewart is silent on electrodes as a matrix of points. DeSilva teaches a biosensor for use in antigen-antibody interaction comprising a discontinuous film of platinum islands (matrix) of 60-120 Å diameter as electrodes on a silicon dioxide substrate (p. 677, ¶ 1), and that such arrangement is extremely sensitive to small changes in electrical properties of the material (analyte) between the islands. One of ordinary skill would find obvious from the teaching of DeSilva the use and desirability of

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such islands in order to detect changes in impedance (capacitive component thereof) associated with lower affinity events of antigen-antibody interaction or nucleic acid hybridization.

13. Claim 16 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart as applied to claim 10 above, and further in view of C. Berggren and K-M. Chang et al., U.S. Patent 6,236,096 (herein after Chang).

Ewart is silent on a three electrode capacitive sensor. Such three electrode systems are known in the art and permit measurement of two capacitance values, including that from a sensor and a second from a reference. Berggren teaches a three electrode system for detecting capacitance changes in biosensors (p. 178, ¶ 6). Further, Chang teaches capacitive pressure sensor with a three-prong electrode (col 1, ¶ 1). One of ordinary skill in the art would find obvious to use such three electrode system according to the teachings of Berggren and Chang in the sensor of Ewart in order to provide for local calibration in capacitance, since variations in manufacture across the sensor would degrade resolution in high sensitivity measurements.

14. Claim 18 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart as applied to claim 10 above, and further in view of G.T.A. Kovacs, U.S. Patent 6,682,936 (herein after Kovacs).

For Claim 18, Ewart is silent on the use of the conductive label as a gate for a MOS- or EEPROM-like structure. Kovacs does not teach a conductive label creating a MOS gate

but does teach an array of electrodes on an integrated circuit chip for carrying out multi-step biochemical reactions, an electrode of which is formed above a MOS-photodiode structure within a CMOS circuit (embedded in the semiconductor below the binding sites) (col 4, lines 22-26, col 9, lines 56-60 and Fig. 7). It would have been obvious to one of ordinary skill in the art to use a conductive label as a gate for MOS transducer according to the teaching of Kovacs within the sensor of Ewart in order to provide the advantages in electronic stability of an on-board switch in the circuitry associated with detecting a reaction or binding event.

15. Claims 19-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart as applied to claim 10 above, and further in view of P. Van Gerwen et al., International Conference on Solid-State Sensors and Actuators Chicago, June 16-19, p. 907-910, 1997 (herein after Van Gerwen).

For Claim 19, Ewart is silent on the spacing of electrodes with respect to the size of a single label. Ewart teaches nanoparticles for use in biosensors having diameters less than 1000 nanometers. Van Gerwen teaches spacings of fingers in interdigitated electrodes used in biochemical sensors of 250 nanometers (p. 907, ¶ 3). Knowing the range of spacing available for configuring electrodes, one of ordinary skill in the art would have found obvious to optimize the size of nanoparticles, commercially available in a range of diameters, in order to match or fall under that of the electrode spacing, depending on the need for resistive (calling for a short circuit between electrodes) or capacitive measurements or capacitive component of impedance measurements.

For Claim 20, Ewart and Van Gerwen are silent on the distance between two electrodes. One of ordinary skill in the art would find obvious to optimize such distance ( $d$  in  $C = \epsilon\epsilon_0 A/d$ , the expression for capacitance) in order to provide for optimal signal in capacitance, since such property is inversely proportional to  $d$  and the effective value will change with a change in the dielectric associated with the presence of nanoparticles.

16. Claim 26 is rejected under 35 U.S.C. 103(a) as being unpatentable over Ewart in view of N. Maruno et al., U.S. Patent 5,917,264 (herein after Maruno) and J.

Vangrunderbeek et al., U.S. Patent 6,514,394 (herein after Vangrunderbeek).

For Claim 26, Ewart does not teach use of aluminum electrodes or non-conductive surface formed by alumina. Such materials are known for use in fabrication of electrodes and non-conducting surfaces of electrodes in sensors. N. Maruno teaches a pressure sensor with aluminum electrodes (col 14, lines 45-47) and J. Vangrunderbeek teaches a sensor in which the non-conducting material is made of alumina (col 8, lines 23-24). It would have been obvious to one of ordinary skill in the art to use aluminum for electrodes in order to obtain the advantage of readily available foil for which the thickness and area (and therefore, capacitance) can be easily controlled and to use alumina for non-conducting surfaces in order to provide the advantage available in manufacture associated with vapor deposition.

***Conclusion***

17. The prior art made of record and not relied upon is considered pertinent to applicant's disclosure. H. Berney et al., Sensors and Actuators B 68: 100-108, 2000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to TIMOTHY G. KINGAN whose telephone number is (571)270-3720. The examiner can normally be reached on Monday-Friday, 8:30 A.M. to 5:00 P.M., E.S.T..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jill Warden can be reached on 571 272-1267. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

TGK

/Jill Warden/  
Supervisory Patent Examiner, Art Unit 1797